

Lactose Intolerance

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. FOURCADE*: The patient is a 38-year-old nurse who was admitted to this hospital because of intermittent diarrhea and abdominal pain for the past nine years, increasing over the past one year. She has had ten to twelve bowel movements a day during this period. The stools were described as loose, watery, brown, foul smelling, and occasionally greasy or foamy, sometimes floating. The patient described the abdominal pain as cramping in nature, occurring one to two hours after meals. She also noted that milk caused some abdominal discomfort. In the past year her weight had decreased approximately 15 pounds. She had had no weight loss during the preceding eight years. Three intra-abdominal surgical procedures were confined to pelvic organs. The patient denied bone or joint pain, fever or jaundice. Cultures of the stool have been negative in the past and treatment with corticosteroids for three months was without effect on either diarrhea or pain.

On physical examination the patient was observed to be slim, well-nourished and depressed but in no acute distress. The vital signs and results of the examination of the skin, eyes, tongue, chest and heart were within normal limits. Examination of the abdomen revealed diffuse tenderness but no masses or organ enlargement. Results of blood cell count and urinalysis were within normal limits. Results of all other studies of the feces including examination for occult blood, ova and parasites, were negative. Studies for malabsorption also were negative.

No rise in blood glucose was observed after the patient ingested first 50 grams and then 100 grams

of lactose, whereas with similar doses of glucose, galactose and sucrose a normal rise in blood glucose was observed. About two to six hours after ingesting the lactose, the patient noted severe diarrhea and cramps. Biopsy of the jejunum was attempted but insufficient tissue was obtained. The patient was discharged and appeared more comfortable on a lactose-free diet.

DR. ZBORALSKE*¹: Two upper gastrointestinal and small bowel series were performed. The first of these (Figure 1), using a barium preparation which does not contain sugar, was within normal limits. Contrast material did appear in the colon within 30 minutes, suggesting rapid transit. However in some normal patients barium will appear in the colon within 30 minutes and this cannot be considered unusual. There was no dilatation of the bowel and the barium was dispersed throughout.

Twenty-four hours later the patient was given barium containing 50 grams of lactose. In this study (Figure 2) the small bowel is dilated, and the normal valvular pattern is lost. There is homeogeneity, which suggests increased fluid within the lumen of the small bowel. From the study with lactose there appears to be an increased amount of fluid within the lumen and there is some dilatation of the small bowel, jejunum and ileum.

DR. SMITH*²: Thank you, Dr. Zboralske. This patient, unfortunately, is not here for presentation in person this morning. She was referred to the hospital by Dr. Harry Daniel and Dr. Howard

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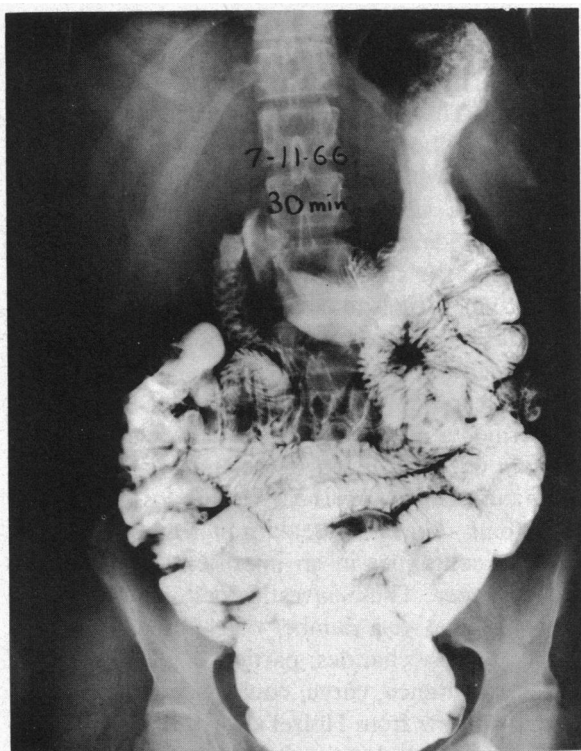


Figure 1.—X-ray film with barium preparation (without sugar).

Shapiro. I wonder if they would care to comment before the main discussion.

DR. SHAPIRO^{*3}: I have no comments to make except to remind everyone concerned that three years ago this patient might have been given the diagnosis of psychogenic diarrhea.

DR. SMITH: This is an intriguing subject which has been prominent in the medical literature in recent years, with increasing understanding of disaccharide intolerance. We are very fortunate to have Dr. Keith Taylor with us today to lead the discussion concerning this patient and this interesting syndrome. Dr. Taylor was originally from England and had his undergraduate and medical training at Oxford University. He is now at Stanford University as Professor of Medicine and chief of the Gastroenterology Section. Dr. Taylor.

DR. TAYLOR^{*4}: Thank you, Dr. Smith. When I was asked to lead the discussion about this interesting patient I explained to Dr. Smith that I was not active, myself, in the exciting field of disaccha-

ridase deficiency and of intolerance to disaccharides. It is one which is developing so rapidly that many of us find the wealth of material presented in the literature somewhat indigestible. A few years ago one would not have considered the question of disaccharide intolerance at all in a patient of this sort. Now perhaps the pendulum is swinging a little too far the other way. I suppose that ultimately we shall find some middle course; this will depend on our capacity to relate available data to any particular patient presenting in this way. Major deficiencies of most studies in this area are the lack of control data, particularly disaccharide tolerance curves and enzyme estimations in jejunal and lower intestinal material, and proper correlation of these parameters with the clinical picture in various groups of patients.

The problem posed by this patient is: "Are her symptoms really caused by a failure specifically to handle lactose?" In order to answer this, we need a few hints in the history; first, are her symptoms brought on by the ingestion of lactose? As you know, in the past, many patients in whom intolerance to milk was reported were thought to have allergic sensitivity to milk proteins. It is only in recent years that the problem of lactose intolerance has been raised. The second question is: "Are her symptoms relieved by exclusion of lactose from the diet?" The patient has had symp-

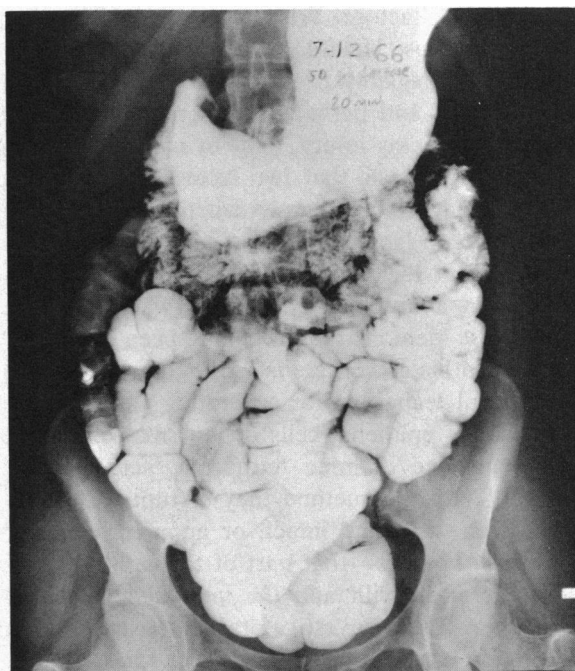


Figure 2.—X-ray film with barium containing 50 gm of lactose.

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toms for nine years, gradually increasing in severity and much worse in the last year. There has been loss of weight and a change in her bowel habit, resulting first in intermittent and later in continuous diarrhea. Does lactose exclusion relieve this? Since the patient was observed to be "depressed," it is difficult to interpret the response to the changes in diet, which were not evaluated by double blind technique. I think this is something we have to consider very seriously in someone with a problem of this type. Thirdly, we have the results of tolerance tests, which could be interpreted as showing a deficiency of lactase activity in the bowel. Finally we would like to have evidence of lactase deficiency by small bowel biopsy, which was quite properly attempted but which did not succeed.

At this point we might consider one or two problems relating to disaccharide absorption and then return to this patient. The problem under consideration today involves the method by which lactose is handled, but other disaccharidases, such as maltase and iso-maltase, are important and might be considered also. When lactose is ingested, it may either be unabsorbed, pass on and be fermented in the lower part of the bowel, or it may be converted to glucose and galactose and transported across the intestinal wall into the blood. In certain situations, particularly in very young children, free lactose may be absorbed and appear in the blood as lactose. When compared with other disaccharidases, lactase, which is a very specific enzyme, is probably present in lowest activity in the gut wall, and perhaps therefore may be most susceptible to any injury, toxic or mechanical. Recent work suggests that two lactases exist and at the moment it is not known whether one or both play a part in lactose digestion.

The exact location of these enzymes has been studied in a number of different ways. Perhaps the nicest demonstrations have been those of Crane and his coworkers in Chicago, who devised a beautiful technique for separating various fractions of the epithelial cells of the small intestine, using ethylene diamine tetraacetic acid (EDTA) buffers. With this method they disrupted the epithelial cell, retaining intact, or apparently intact, the brush borders—that part of the cell that contains the micro-villi and the immediate adjacent structures. These investigators demonstrated that the major part of the activity resides in the components of the mucosa which are found deeper in the villi. The most superficial parts of the tips of

the villi contain maximal disaccharidase activity. In the deeper layers of the epithelium, the deeper layers of the villi and in the crypts the activity is reduced. This has been demonstrated also with labelled antibodies directed against specific disaccharidases, which are taken up by the brush borders of the small intestinal epithelial cells. This kind of evidence suggests very strongly that this location is the site of the highest concentration of the enzymes, the site of hydrolysis of disaccharides. This has been shown also by various labelled sugar experiments.

For years, particularly in children, the concept of fermentative diarrhea has been entertained. Certain children appear to tolerate sugars poorly, as manifested in diarrhea, weight loss and other symptoms. The first breakthrough was by Holzel and his colleagues in an important and now historical paper. These investigators showed for the first time that in a number of children with intolerance to disaccharides, particularly lactose, a flat lactose tolerance curve could be demonstrated. The idea grew from Holzel's work that these findings were due to lactase deficiency in the gut wall and that fermentative diarrhea of this type might be associated with a lactase deficiency. However, for some time, Holzel insisted that these were in fact two different types of intolerance to lactose in infancy. One type, which he described as lactose intolerance, was associated with lactosuria, with a normal lactose tolerance curve and severe symptoms with ingestion of lactose. The second type represented a deficiency of lactase in the gut wall, and was associated with milder symptoms and absence of lactosuria. More recently, this separation has not been endorsed, and many investigators in this field today, I believe, would consider the idea of lactose intolerance specifically in terms of lactase deficiency.

The syndromes associated with lactose intolerance are many. Congenital lactase deficiency, occurring in infants, with or without lactosuria has been mentioned. Several questions about this syndrome arise. Is this truly congenital? Is it ever familial? Is it in fact genetically determined? The present evidence is extremely difficult to interpret. Studies in this field have been so few in total number that it is extremely difficult to dissociate environmental factors from genetic factors, and at the moment this point seems to be unproved.

Secondary lactase deficiency includes a number of clinical situations: Lactase deficiency in association with intestinal infection, which has been

observed frequently in children and appears to be quite non-specific; lactose intolerance associated with malnutrition, particularly in infants; and that seen in association with gross changes of the intestinal mucosa produced by gluten-induced enteropathy. In these latter conditions there is in fact lack of many disaccharidases, and lactase particularly is the enzyme most deficient.

After extensive small bowel resection a reduction in the total amount of lactase is expected and the distribution of lactase along the gut seems to be an important factor. One may expect to find low lactase activity at the region of the ligament of Treitz. This activity is well maintained throughout the first half of the small intestine, but with some tendency toward diminution in the distal part of the small bowel. This is a very important point in deciding where to take a specimen for biopsy and what interpretation to place on the biopsy observations.

The question of lactose intolerance associated with milk intolerance in adults is a difficult one. The best way to dissociate the intolerance toward milk due to protein sensitivity and that due to lactose intolerance, is to determine by a series of feeding experiments, preferably done by double blind techniques, that only lactose will produce symptoms and milk proteins *per se* will not do so. A useful source of milk protein is cheese, which contains little lactose. In the future the use of purified milk protein may help to differentiate these two possibilities.

Next is the question of lactose intolerance in association with chronic inflammatory disease of the bowel, both of the small bowel and of the large bowel. There have now been a number of studies reporting diminution of enzyme activity in these various diseases. The role of this disaccharidase deficiency, either in the continuation of the disease or exacerbation of the disease process, is uncertain. Again we still lack sufficiently well controlled studies. Lactose intolerance may also occur in cystic fibrosis, in severe infestations with *Giardia*, and with beta-lipoprotein deficiency. Finally we have the recent observations that lactase deficiency may develop in the gut wall of women taking oral contraceptives, and disappear when use of these steroids is discontinued.

A number of factors will affect the activity of lactase in the bowel wall. First, the question of age. There seems to be in fact some minor variation with age (although this is much more appar-

ent in certain laboratory animals who show very clear evidence of a decrease in lactase after weaning). This is not nearly so apparent in man. The next question relates to the expression of enzyme activity—the units of lactase activity. This activity relates to the rate of destruction by hydrolysis of the appropriate substrate in terms of micromoles released at 37°C, expressed in relation to the weight of the tissue which contains the enzyme. This is usually in terms of wet weight of the tissue, but some investigators have used dry weight, and some others have used protein content as a reference. This leads to some confusion and there is little agreement at the moment as to which is the most appropriate reference to use.

Next the question of race and environmental factors has to be considered. It has been shown recently in Africa that intestinal lactase activities in adjacent tribes is quite different, and at the moment this has not been related fully to any particular dietary habits. Yet these tribes are quite close ethnically. One study of lactose intolerance included a mixed group of Caucasians and Negroes. Negroes were apparently symptom-free but had low enzyme activity. This suggests that there may actually be racial differences in enzyme activity.

The question of diet has not been resolved. Some evidence exists in animals that diet can induce changes in the concentration of these enzymes, particularly of lactase. There is no evidence as yet that suggests this situation in man.

The question of tolerance curves then arises. The early demonstration by Holzel and others suggested that in the absence of diabetes a flat lactose tolerance curve indicated a lactase deficiency in the gut. There was no biopsy confirmation. Attempts have been made to correlate the enzyme activities and the lactose tolerance curves. At first good correlation was apparent. It was also noted that some patients who were asymptomatic would have both flat lactose tolerance curves and hypolactasia defined by multiple observations. However, more recently there have been a number of studies to show this is no longer true. In a recent study, 16 patients with normal gastrointestinal function were given both 50 and 100 gm lactose loads by mouth. Three of these 16 patients had an increase in blood glucose of less than 10 mg per 100 ml following ingestion of the lactose. Yet biopsy specimens from these patients showed no deficiency of lactase. This suggests that we still

need to know a great deal more about the actual correlation of lactose absorption and the activity of lactase in the gut.

We come finally to the studies which have been done on lactase activity in biopsy material. Here again the initial studies looked extremely encouraging, with good correlation between clinical symptoms and lactase activity in the gut wall. However, recently it has been shown that many persons who appear to have hypolactasia have no symptoms, either with a normal diet or with lactose ingestion. Furthermore some control subjects have been found to have very low or absent lactase activity in the gut wall but no symptoms.

It is with patients similar to the patient presented today that we are very much concerned. The question now remains as to whether her symptoms are due to lactose intolerance and in turn to hypolactasia, or are the data which have been obtained explicable in other ways—such as changes in gastric emptying, changes of intestinal transport, or other diseases of the gastrointestinal tract which have not yet been found. I must confess I found the x-ray films extremely impressive—an excellent demonstration of a response to lactose in the barium solution. Did the patient know that lactose was present? I feel I must ask you that at this stage.

DR. FOURCADE: Yes, she did know that lactose was being added. Also of importance is the fact that we did not have an opportunity to test some normal subjects.

DR. TAYLOR: This question is very important. Gastric emptying can be delayed with hypertonic solutions in the stomach. This may explain why the use of 50 gm and 100 gm lactose loads may give divergent results in subjects studied with both doses. Some patients show a higher peak of blood glucose after 50 gm and some show it after 100 gm. This can really only be explained in terms of the weight of material presented to the gut wall. Another point is that many of us find the taking of hypertonic solutions nauseating, as I did the first time I took 25 gm of xylose.

Why does lactose produce diarrhea, if it does? The possibilities include a lower pH and probably increased lactic acid in the stool. In some patients

the colon seems to do a good job of removing the lactic acid, and one may not always find this in established cases of lactose intolerance. It is conceivable that lactose affects the flora of the gut in some way.

I think I have said quite enough, Dr. Smith. I have said nothing which would allow any firm diagnosis to be made in the patient presented but I hope I have stimulated thinking about these problems. The days when the gastroenterologist could just talk about the irritable bowel syndrome and nervous diarrhea appear, fortunately, to be coming to an end. Thank you very much.

DR. SMITH: I think Dr. Taylor has given us an excellent summary of this complex subject, and also in a very quiet and gentle way has let us know that our evidence is inadequate to support the diagnosis listed in the protocol. I would like to throw this open for discussion and comment.

DR. WILLIAMS*⁵: Since the pH optimum of most of the disaccharidases is close to 6.5, does the pH of the bowel contents affect enzyme activity?

DR. TAYLOR: I think this is an extremely important point, and it may help us to explain why primary disturbances of the bowel may lead to observed intolerance in the handling of lactose. But I do not think we have adequate measurement of local pH conditions in the bowel. Perhaps with new telemetering devices we shall obtain more information about pH.

PHYSICIAN IN AUDIENCE: There is apparently some evidence that the severity of symptoms with lactose is proportional to the amount of ingested lactose. Do you feel that the 100 gram test offers sufficient stress to bring out a flat curve?

DR. TAYLOR: I think it would be very difficult to administer more than 1.5 gm per kg of body weight, which is about as much lactose as anyone can tolerate. No one, so far as I know, has pursued this further, as has been done for fat ingestion; that is, to gradually increase the quantity of lactose until absorption levels off and an excess appears in the stool. I am not aware of any studies of that sort, but I would be pleased to hear of them.

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